PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

# PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
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in its capacity as elected Office

| | |
|---|---|
| **Date of mailing** (day/month/year)<br>22 March 2000 (22.03.00) | |
| **International application No.**<br>PCT/EP99/05744 | **Applicant's or agent's file reference**<br>BET 99/0674 |
| **International filing date** (day/month/year)<br>29 July 1999 (29.07.99) | **Priority date** (day/month/year)<br>29 July 1998 (29.07.98) |
| **Applicant**<br>SCHWARTZ, Jean-Charles et al | |

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   23 February 2000 (23.02.00)

   [ ] in a notice effecting later election filed with the International Bureau on:

   _____

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61R 31/4453, 31/40, 31/445, 31/138

A2

(11) International Publication Number: **WO 00/06254**

(43) International Publication Date: 10 February 2000 (10.02.00)

(21) International Application Number: PCT/EP99/05744

(22) International Filing Date: 29 July 1999 (29.07.99)

(30) Priority Data:

| | | |
|---|---|---|
| 98401944.8 | 29 July 1998 (29.07.98) | EP |
| 98403351.4 | 31 December 1998 (31.12.98) | EP |

(71) Applicant *(for all designated States except US)*: SOCIETE CIVILE BIOPROJET [FR/FR]; 30, rue des Francs Bourgeois, F–75003 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SCHWARTZ, Jean–Charles [DE/FR]; 9, villa Seurat, F–75014 Paris (FR). ARRANG, Jean–Michel [FR/FR]; 3, avenue des Acacias, F–91410 Dourdan (FR). GARBARG, Monique [FR/FR]; 26, boulevard Gouvion Saint Cyr, F–75017 Paris (FR). LECOMTE, Jeanne–Marie [FR/FR]; 30, rue des Francs Bourgeois, F–75003 Paris (FR). LIGNEAU, Xavier [FR/FR]; 10, rue des Tanneries, F–75013 Paris (FR). SCHUNACK, Walter, G. [DE/DE]; Spanische Allee 95, D–14129 Berlin (DE). STARK, Holger [DE/DE]; Heiligendammer Strasse 11, D–14199 Berlin (DE). GANELLIN, Charon, Robin [GB/GB]; Kinwood Briary Wood End, Welwyn, Hert AL6 0TD (GB). LEURQUIN, Fabien [FR/GB]; 49 Chilton Street, London E2 6DZ (GB). SIGURD, Elz [DE/DE]; Albulaweg 7a, D–12107 Berlin (DE).

(74) Agent: OBOLENSKY, Michel; Cabinet Lavoix, 2, place d'Estienne d'Orves, F–75441 Paris Cedex 09 (FR).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

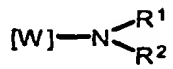
**Published**

*Without international search report and to be republished upon receipt of that report.*

(54) Title: NON–IMIDAZOLE ALKYLAMINES AS HISTAMINE $H_3$–RECEPTOR LIGANDS AND THEIR THERAPEUTIC APPLICATIONS

(57) Abstract

Use of a compound of formula (A), wherein:



(A)

W is a residue which imparts antagonistic and/or agonistic activity at histamine $H_3$–receptors when attached to an imidazole ring in 4(5) position; $R^1$ and $R^2$ may be identical or different and represent each independently a lower alkyl or cycloalkyl, or taken together with the nitrogen atom to which they are attached, a saturated nitrogen–containing ring (i) as defined, a non–aromatic unsaturated nitrogen–containing ring (ii) as defined, a morpholino group, or a N–substituted piperazino group as defined for preparing medicaments acting as antagonists and/or agonists at the $H_3$–receptors of histamine.

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# INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 99/05744

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4453 A61K31/40 A61K31/445 A61K31/138

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | BRANDES L J ET AL: "New evidence that the antiestrogen binding site may be a novel growth-promoting histamine receptor (?H3) which mediates the antiestrogenic and antiproliferative effects of tamoxifen" BIOCHEM. BIOPHYS. RES. COMMUN. (BBRCA9,0006291X);1986; VOL.134 (2); PP.601-8, XP002123595 Univ. Manitoba;Manitoba Inst. Cell Biol.; Winnipeg; R3E 0V9; MB; Can. (CA) the whole document --- -/-- | 16-28 |

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 November 1999 | 04.01.00 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Scruton-Evans, I |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | GANELLIN C R ET AL: "Synthesis of potent non-imidazole histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1998; VOL.331 (12); PP.395-404, XP002123596 Univ. London;Dep. Chemistry, College London, Christopher Ingold Lab.; London; WC1H OAJ; UK (GB) | 16-28 |
| P,Y | the whole document<br>--- | 16-28 |
| A | KIEC-KONONOWICZ K ET AL: "Azines and diazines as potential histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.445-50, XP002123597 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL) the whole document<br>--- | 16-28 |
| A | KIEC-KONONOWICZ K ET AL: "Pyrazoles as potential histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.469-72, XP002123598 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL) the whole document<br>--- | 16-28 |
| Y | ARRANG J M ET AL: "Actions of betahistine at histamine receptors in the brain" EUR. J. PHARMACOL. (EJPHAZ,00142999);1985; VOL.111 (1); PP.73-84, XP002123599 Cent. Paul Broca;Unite Neurobiol.; Paris; 75014; Fr. (FR) the whole document<br>--- | 16-28 |
| Y | CHEMICAL ABSTRACTS, vol. 124, no. 23, 3 June 1996 (1996-06-03) Columbus, Ohio, US; abstract no. 308211, IMAIZUMI M ET AL: "Effects of betahistine, a histamine H1 agonist and H3 antagonist, in a light/dark test in mice" XP002123600 abstract & METHODS FIND. EXP. CLIN. PHARMACOL. (MFEPDX,03790355);1996; VOL.18 (1); PP.19-24, Yamasa Corporation;Biology Laboratory; Choshi; Japan (JP)<br>--- | 16-28 |
| | -/-- | |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CHEMICAL ABSTRACTS, vol. 123, no. 1, 3 July 1995 (1995-07-03) Columbus, Ohio, US; abstract no. 000292, STARK H ET AL: "New potent histamine H3-receptor antagonists of the amide type" XP002123601 abstract & EUR. J. PHARM. SCI. (EPSCED,09280987);1995; VOL.3 (2); PP.95-104, Institut fuer Pharmazie, Freie Universitaet Berlin, Koenigin-Luise-Strasse 2+4;Berlin; 14195; Germany (DE) --- | 16-28 |
| Y | CHENEY L C ET AL: "Alkylaminoalkyl Ethers of the Benzylphenols" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,US,AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 71, page 60-64 XP002086293 ISSN: 0002-7863 see page 60, compound III and last paragraph of page 60 ----- | 16-28 |

# INTERNATIONAL SEARCH REPORT

Inte. ational application No.
PCT/EP 99/05744

**Box I Observati ns where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See further information sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

16 - 28, 78 (partially)

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15,29-38,46-50,54,70,72,73,79-88

1) Present claims 1-15 relate to a use of a compound defined by reference to a desirable characteristic or property, namely that W is a residue that imparts antagonistic and/or agonistic activtiy at histamine H3-receptors when attached to an imidazole ring in 4(5) position. The claims cover the use of all such compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound to be used by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

2) Present claims 29-38,46-50,54,70,72 and 79-88 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Specifically, for claim 54, AViii may be absent, Xviii may be ,Y may be absent and R4viii may be H, such that none of the groups has any recognisable common definition.

3) Present claim 73 relates to the use of a compound of the formula XVI, wherein Zxvi may optionally comprise other substituents selected such that the activtiy of the derivative is not negatively affected. The claims cover the use of all compounds of formula XVI having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, this claim so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, this claim also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear,supported and disclosed, namely those parts relating to the claims 16-28.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 16-28,78(partially)

Use of compounds of the formula I for the preparation of a medicament acting as a ligand of the histamine H3-receptors

2. Claims: 39-45,78(partially)

Use of compounds of formulae III or IV for the preparation of a medicament acting as a ligand of the histamine H3-receptors

3. Claims: 51-53,78(partially)

Use of the compounds of formula VII for the preparation of a medicament acting as a ligand on the hiatamine H3-receptors.

4. Claims: 55-56,78(partially)

Use of a compound of the formulae VIIIa or VIIIb for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

5. Claims: 57-60,78(partially)

Use of compounds of formulae IX or X for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

6. Claims: 61-67,78(partially)

Use of a compound of formula XI or XIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

7. Claims: 68-69, 78(partially)

Use of a compound of the formula XIIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

8. Claims: 71,78(partially)

use of a compound of the formulae XIVa,XIVb or XIVcfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

9. Claims: 74,78(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of a compound of the formula XVII for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

10. Claims: 75-77,78(partially)

Use of a compound of the formula V for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

09/622199

**PCT**

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)


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(74) Agent: OBOLENSKY, Michel; Cabinet Lavoix, 2, place d'Estienne d'Orves, F–75441 Paris Cedex 09 (FR).



(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(88) Date of publication of the international search report:
4 May 2000 (04.05.00)


(54) Title: NON–IMIDAZOLE ALKYLAMINES AS HISTAMINE $H_3$–RECEPTOR LIGANDS AND THEIR THERAPEUTIC APPLICATIONS


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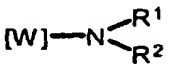

(A)

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| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

Q2

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rul s 43 and 44)

| Applicant's or agent's file reference | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
|---|---|---|
| BET 99/0674 | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/EP 99/05744 | 29/07/1999 | 29/07/1998 |
| Applicant | | |
| SOCIETE CIVILE BIOPROJET et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/05744

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See further information sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

16 - 28, 78 (partially)

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.2

Claims Nos.: 1-15,29-38,46-50,54,70,72,73,79-88

1) Present claims 1-15 relate to a use of a compound defined by reference to a desirable characteristic or property, namely that W is a residue that imparts antagonistic and/or agonistic activtiy at histamine H3-receptors when attached to an imidazole ring in 4(5) position. The claims cover the use of all such compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound to be used by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

2) Present claims 29-38,46-50,54,70,72 and 79-88 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Specifically, for claim 54, AViii may be absent, Xviii may be ,Y may be absent and R4viii may be H, such that none of the groups has any recognisable common definition.

3) Present claim 73 relates to the use of a compound of the formula XVI, wherein Zxvi may optionally comprise other substituents selected such that the activtiy of the derivative is not negatively affected. The claims cover the use of all compounds of formula XVI having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, this claim so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, this claim also lacks clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear,supported and disclosed, namely those parts relating to the claims 16-28.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 16-28,78(partially)

   Use of compounds of the formula I for the preparation of a medicament acting as a ligand of the histamine H3-receptors

2. Claims: 39-45,78(partially)

   Use of compounds of formulae III or IV for the preparation of a medicament acting as a ligand of the histamine H3-receptors

3. Claims: 51-53,78(partially)

   Use of the compounds of formula VII for the preparation of a medicament acting as a ligand on the hiatamine H3-receptors.

4. Claims: 55-56,78(partially)

   Use of a compound of the formulae VIIIa or VIIIb for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

5. Claims: 57-60,78(partially)

   Use of compounds of formulae IX or X for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

6. Claims: 61-67,78(partially)

   Use of a compound of formula XI or XIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

7. Claims: 68-69, 78(partially)

   Use of a compound of the formula XIIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

8. Claims: 71,78(partially)

   use of a compound of the formulae XIVa,XIVb or XIVcfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

9. Claims: 74,78(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of a compound of the formula XVII for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

10. Claims: 75-77,78(partially)

Use of a compound of the formula V for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/05744

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4453 A61K31/40 A61K31/445 A61K31/138

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | BRANDES L J ET AL: "New evidence that the antiestrogen binding site may be a novel growth-promoting histamine receptor (?H3) which mediates the antiestrogenic and antiproliferative effects of tamoxifen" BIOCHEM. BIOPHYS. RES. COMMUN. (BBRCA9,0006291X);1986; VOL.134 (2); PP.601-8, XP002123595 Univ. Manitoba;Manitoba Inst. Cell Biol.; Winnipeg; R3E 0V9; MB; Can. (CA) the whole document --- -/-- | 16-28 |

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 November 1999 | 04/12/99 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Scruton-Evans, I |

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | GANELLIN C R ET AL: "Synthesis of potent non-imidazole histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1998; VOL.331 (12); PP.395-404, XP002123596 Univ. London;Dep. Chemistry, College London, Christopher Ingold Lab.; London; WC1H OAJ; UK (GB) | 16-28 |
| P,Y | the whole document<br>--- | 16-28 |
| A | KIEC-KONONOWICZ K ET AL: "Azines and diazines as potential histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.445-50, XP002123597 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL) the whole document<br>--- | 16-28 |
| A | KIEC-KONONOWICZ K ET AL: "Pyrazoles as potential histamine H3-receptor antagonists" ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.469-72, XP002123598 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL) the whole document<br>--- | 16-28 |
| Y | ARRANG J M ET AL: "Actions of betahistine at histamine receptors in the brain" EUR. J. PHARMACOL. (EJPHAZ,00142999);1985; VOL.111 (1); PP.73-84, XP002123599 Cent. Paul Broca;Unite Neurobiol.; Paris; 75014; Fr. (FR) the whole document<br>--- | 16-28 |
| Y | CHEMICAL ABSTRACTS, vol. 124, no. 23, 3 June 1996 (1996-06-03) Columbus, Ohio, US; abstract no. 308211, IMAIZUMI M ET AL: "Effects of betahistine, a histamine H1 agonist and H3 antagonist, in a light/dark test in mice" XP002123600 abstract & METHODS FIND. EXP. CLIN. PHARMACOL. (MFEPDX,03790355);1996; VOL.18 (1); PP.19-24, Yamasa Corporation;Biology Laboratory; Choshi; Japan (JP)<br>--- | 16-28 |
| | -/-- | |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | CHEMICAL ABSTRACTS, vol. 123, no. 1, 3 July 1995 (1995-07-03) Columbus, Ohio, US; abstract no. 000292, STARK H ET AL: "New potent histamine H3-receptor antagonists of the amide type" XP002123601 abstract & EUR. J. PHARM. SCI. (EPSCED,09280987);1995; VOL.3 (2); PP.95-104, Institut fuer Pharmazie, Freie Universitaet Berlin, Koenigin-Luise-Strasse 2+4;Berlin; 14195; Germany (DE) --- | 16-28 |
| Y | CHENEY L C ET AL: "Alkylaminoalkyl Ethers of the Benzylphenols" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,US,AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 71, page 60-64 XP002086293 ISSN: 0002-7863 see page 60, compound III and last paragraph of page 60 ----- | 16-28 |

09/622199

# PATENT COOPERATION TREATY

RCD 19 JUL 2000

WIPO PCT

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| BET 99/0674 | | |
| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
| PCT/EP99/05744 | 29/07/1999 | 29/07/1998 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/4453 | | |
| Applicant<br>SOCIETE CIVILE BIOPROJET et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Auth rity (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 23/02/2000 | 17.07.2000 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized officer<br>Scruton-Evans, I<br>Telephone No. +49 89 2399 8272 |

Form PCT/IPEA/409 (cover sheet) (January 1994)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/05744

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-153 as originally filed

**Claims, No.:**

1-88 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they hav been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-15,29-38,46-50,54,70,72,73,79-88.

b cause:

☐ the said international application, or the said claims Nos. relate to the following subject matter which do s not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-15,29-38,46-50,54,70,72,73,79-88.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   **see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 16-28,78(partially).

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | |
| | No: | Claims | 16,18,23,24 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 16-28,78(partially) |
| Industrial applicability (IA) | Yes: | Claims | 16-28,78 (partially) |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Re Item III**

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Present claims 1-15 relate to a use of a compound defined by reference to a desirable characteristic or property, namely that W is a residue that imparts antagonistic and/or agonistic activity at histamine H3-receptors when attached to an imidazole ring in 4(5) position.

The claims cover the use of all such compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound to be used by reference to a result to be achieved. Again, this lack of clarity in the present case was such as to render a meaningful search over the whole of the claimed scope impossible.

2) Present claims 29-38,46-50,54,70,72 and 79-88 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arose to such an extent as to render a meaningful search of the claims impossible. Specifically, for claim 54, AViii may be absent, Xviii may be ,Y may be absent and R4viii may be H, such that none of the groups has any recognisable common definition.

3) Present claim 73 relates to the use of a compound of the formula XVI, wherein Zxvi may optionally comprise other substituents selected such that the activity of the derivative is not negatively affected. The claims cover the use of all compounds of formula XVI having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, this claim so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible. Independent of the above reasoning, this claim also lacks

clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case was such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search was carried out for those parts of the claims which appeared to be clear, supported and disclosed, namely those parts relating to the claims 16-28.

The Applicant's attention is drawn to the fact that claims, or parts of claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched.

**Re Item IV**

Lack of unity of invention

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 16-28,78(partially)

Use of compounds of the formula I for the preparation of a medicament acting as a ligand of the histamine H3-receptors

2. Claims: 39-45,78(partially)

Use of compounds of formulae III or IV for the preparation of a medicament acting as a ligand of the histamine H3-receptors

3. Claims: 51-53,78(partially)

Use of the compounds of formula VII for the preparation of a medicament acting as a ligand on the histamine H3-receptors.

4. Claims: 55-56,78(partially)

Use of a compound of the formulae VIIIa or VIIIb for the preparation of a medicament

acting as a ligand of the histamine H3-receptors.

5. Claims: 57-60,78(partially)
Use of compounds of formulae IX or X for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

6. Claims: 61-67,78(partially)
Use of a compound of formula XI or XIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

7. Claims: 68-69, 78(partially)
Use of a compound of the formula XIIIfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

8. Claims: 71,78(partially)
use of a compound of the formulae XIVa,XIVb or XIVcfor the preparation of a medicament acting as a ligand of the histamine H3-receptors.

9. Claims: 74,78(partially)
Use of a compound of the formula XVII for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

10. Claims: 75-77,78(partially)
Use of a compound of the formula V for the preparation of a medicament acting as a ligand of the histamine H3-receptors.

The present application is directed to the use of compounds in the preparation of a medicament acting as a ligand of the histamine H3-receptors. The compounds all fall within the general formula A of claim 1.
For the purposes of unity of invention, Rule 13.1 PCT stipulates that an international application must relate to one invention only or to a group of inventions so linked as to form a single general (inventive) concept. A lack of unity may either be evident a priori from the skilled person's own general knowledge i.e. before the claims have been considered in conjunction with the state of the art established during the search, or may become evident only a posteriori in the light of the prior art.

The Markush formula A of claim 1 assembles all the different compounds wherein W is a residue which imparts antagonistic and/or agonistic activity at histamine H3-receptors when attached to an imidazole ring in 4(5)-position. All of the dependent claims then claim variants of W. However, all of these groups of inventions do not form a single general inventive concept, as the compounds for which the use is claimed do not form a recognised class of compounds.

According to Rule 13.2 PCT, an international patent application may relate to a group of inventions if there was a "technical relationship" among those inventions involving one or more of the same or corresponding "special technical features". Rule 13.1 PCT does not simply require some link between a group of inventions claimed in an international patent application, but a common inventive concept.

In the present application, there is no common special technical feature, as the only common feature is the NR1R2 group in the compounds to be used. It is assumed from the wording of the application that this NR1R2 group has replaced the imidazole group in known H3 antagonists/agonists, but the known compounds did not in themselves represent a unitary class of compounds.

In the present application neither of the conditions of common technical problem or single technical concept is satisfied, and thus there is a lack of unity within the meaning of Rule 13 PCT, and the different inventions, not belonging to a common inventive concept are formulated as different subjects pursuant to Article 17(3)(a) PCT in the order chosen by the Applicant.

In response to the invitation to pay additional search fees, no response was made in due time, and thus the international examination is carried out for that subject matter searched, i.e. subject 1, claims 16-28,78(partially).

**Re Item V**

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the Search Report are referred to in this communication;

D1: BRANDES L J ET AL: 'New evidence that the antiestrogen binding site may be a novel growth-promoting histamine receptor (?H3) which

mediates the antiestrogenic and antiproliferative effects of tamoxifen' BIOCHEM. BIOPHYS. RES. COMMUN. (BBRCA9,0006291X);1986; VOL.134 (2); PP.601-8, XP002123595 Univ. Manitoba;Manitoba Inst. Cell Biol.; Winnipeg; R3E 0V9; MB; Can. (CA)

D2: CHEMICAL ABSTRACTS, vol. 124, no. 23, 3 June 1996 (1996-06-03) Columbus, Ohio, US; abstract no. 308211, IMAIZUMI M ET AL: 'Effects of betahistine, a histamine H1 agonist and H3 antagonist, in a light/dark test in mice' XP002123600 & METHODS FIND. EXP. CLIN. PHARMACOL. (MFEPDX,03790355);1996; VOL.18 (1); PP.19-24, Yamasa Corporation;Biology Laboratory; Choshi; Japan (JP)

D3: CHEMICAL ABSTRACTS, vol. 123, no. 1, 3 July 1995 (1995-07-03) Columbus, Ohio, US; abstract no. 000292, STARK H ET AL: 'New potent histamine H3-receptor antagonists of the amide type' XP002123601 & EUR. J. PHARM. SCI. (EPSCED,09280987);1995; VOL.3 (2); PP.95-104, Institut fuer Pharmazie, Freie Universitaet Berlin, Koenigin-Luise-Strasse 2+4;Berlin; 14195; Germany (DE)

D4: GANELLIN C R ET AL: 'Synthesis of potent non-imidazole histamine H3- receptor antagonists' ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1998; VOL.331 (12); PP.395-404, XP002123596 Univ. London;Dep. Chemistry, College London, Christopher Ingold Lab.; London; WC1H OAJ; UK (GB)

D5: KIEC-KONONOWICZ K ET AL: 'Azines and diazines as potential histamine H3-receptor antagonists' ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.445-50, XP002123597 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL)

D6: KIEC-KONONOWICZ K ET AL: 'Pyrazoles as potential histamine H3- receptor antagonists' ARCH. PHARM. (WEINHEIM, GER.) (ARPMAS,03656233);1995; VOL.328 (5); PP.469-72, XP002123598 Jagiellonian Univ.;Dep. Chemical Technology of Drugs; Krakow; 30-688; Pol. (PL)

D7: ARRANG J M ET AL: 'Actions of betahistine at histamine receptors in the brain' EUR. J. PHARMACOL. (EJPHAZ,00142999);1985; VOL.111 (1); PP.73-84, XP002123599 Cent. Paul Broca;Unite Neurobiol.; Paris; 75014; Fr. (FR)

D8: CHENEY L C ET AL: 'Alkylaminoalkyl Ethers of the Benzylphenols' JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,US,AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 71, page 60-64 XP002086293 ISSN: 0002-7863

Document D4 was published after the priority date of the present application (published on 23.12.98, priority date of application 29.07.98), and thus until such a time as the priority document has been examined as to its validity, it's relevance cannot be assessed.

Novelty

Claims 16-28 are concerned with the use of compounds of the formula I in the preparation of a medicament acting as a ligand of the histamine H3 receptors.

D1 discloses DPPE, falling within the scope of claim 16 as a H1 antagonist, and states that it might be a prototype H3-antagonist. This would appear to be prejudicial to the novelty of claims 16,18,23 and 24. D2 and D7 disclose betahistine, an H3 antagonist, which differs structurally in that it is a pyridine derivative, D3 discloses amides as H3 antagonists, D5 Azines and diazines, D6 pyrazoles and D8 compounds falling within the structural scope of claim 16 but mentioning only antihistaminic generally. Article 33(2) thus does not appear to have been satisfied.

Inventive step

The problem underlying the present application is considered to have been the provision of compounds which act as ligands of the histamine H3 receptors. The solution provided by the Applicant is the use of the compounds of claim 16 formula I. However, given D1and the known use of betahistine it is to be considered to have been obvious to have expected this activity for at least certain of the compounds, and Article 33(3) of the PCT is not considered to have been satisfied.

The use of the expressions "lower", "aryl", etc are not considered to be compatible with compounds which are to have a specific ligand receptor

activity, and these terms should be more precisely defined according to the description, page 6.